



#49

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants: Christine L. Brakel et al. )  
Serial No. 08/479,999 ) Group Art Unit: 1631  
Filed: June 28, 1994 ) Ex'r: Ardin H. Marschel, Ph.D.  
Title: MODIFIED NUCLEOTIDE COMPOUNDS)  
(As Previously Presented) )

527 Madison Avenue, 9th Floor  
New York, New York 10022  
December 26, 2001

**FILED VIA EXPRESS MAIL**

Honorable Commissioner  
of Patents and Trademarks  
Washington, D.C. 20231

**AMENDMENT UNDER 37 C.F.R. §1.116  
(IN RESPONSE TO THE SEPTEMBER 26, 2000 OFFICE ACTION)**

Dear Sirs:

Please enter this response (Amendment Under 37 C.F.R. §1.116) to the Office Action mailed on September 26, 2000 in connection with the above-identified application. A response to the September 26, 2000 Office Action was originally due by December 26, 2000. This response is accompanied by a Petition Under 37 C.F.R. §1.137(b) and authorization for the fee therefor. Accordingly, upon granting of Applicants' Petition, this response (Amendment) will be considered as having been timely filed.

**RECEIVED**

JAN 0 8 2002

OFFICE OF PETITIONS

Christine L. Brakel et al.

Serial No. 08/479,999

Filed: June 28, 1994

Page 2 [Amendment Under 37 C.F.R. §1.116 (In Response To The September 26, 2000 Office Action) - December 26, 2001]

---

EXPRESS MAIL CERTIFICATE	
"Express Mail" Label No.	<u>EL491424303US</u>
Deposit Date	<u>December 26, 2001</u>
I hereby certify that this paper and the attachments herein are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington DC 20231.	
	<u>DEC 26 2001</u>
Ronald C. Fedus	Date
Reg. No. 32,567	

Christine L. Brakel et al.  
Serial No. 08/479,999

Filed: June 28, 1994

Page 3 [Amendment Under 37 C.F.R. § 1.116 (In Response To The September 26, 2000 Office Action) - December 26, 2001]



**KINDLY AMEND THIS APPLICATION AS FOLLOWS:**

**In The Title:**

Please substitute the following title of the invention:

-- MODIFIED RNase H NUCLEOTIDE COMPOUNDS -- .

**In the Claims:**

Please enter replacement claims 1, 18, 19, 21, 37, 41 and 51 as follows:

**Clean Version of Replacement Claims**

1. (Four Times Amended) A modified RNase H resistant nucleotide compound which includes at least one component selected from the group consisting of  $MN_3M$ ,  $B(N)_xM$  and  $M(N)_xB$  wherein

N is a phosphodiester-linked modified or unmodified 2'-deoxynucleoside moiety; provided that at least one N is a phosphodiester-linked unmodified 2'-deoxynucleoside moiety;

M is a moiety that confers endonuclease resistance on said component and that contains at least one modified or unmodified nucleic acid base;

B is a moiety that confers exonuclease resistance to the terminus to which it is attached; and

x is an integer of at least 2.

Christine L. Brakel et al.

Serial No. 08/479,999

Filed: June 28, 1994

Page 4 [Amendment Under 37 C.F.R. §1.116 (In Response To The September 26, 2000 Office Action) - December 26, 2001]

18. (Twice Amended) The modified nucleotide compound of claim 1 which includes at least one sequence of the formula  $M(N)_xB$  wherein B is modified or unmodified 2',3'-dideoxyribose nucleotide.

19. (Twice Amended) The modified nucleotide compound of claim 1 wherein x is an integer selected from the group consisting of 2 or 2.

21. (Four Times Amended) A method of inhibiting the function of an RNA, which comprises:

contacting said RNA, under conditions permissive of hybridization, with a modified RNase H resistant nucleotide compound which includes at least one complementary component selected from the group consisting of  $MN_3M$ ,  $B(N)_xM$  and  $M(N)_xB$  wherein:

N is a phosphodiester-linked modified or unmodified 2'-deoxynucleoside moiety; provided that at least one N is a phosphodiester-linked unmodified 2'-deoxynucleoside moiety;

M is a moiety that confers endonuclease resistance on said component and that contains at least one modified or unmodified nucleic acid base;

B is a moiety that confers exonuclease resistance to the terminus to which it is attached; and

x is an integer of at least 2.

37. (Twice Amended) The method of claim 21 wherein the RNA is contacted with a compound which includes at least one sequence of the formula  $M(N)_xB$  wherein B is modified or unmodified 2',3'-dideoxyribose nucleotide.

Christine L. Brakel et al.

Serial No. 08/479,999

Filed: June 28, 1994

Page 5 [Amendment Under 37 C.F.R. §1.116 (In Response To The September 26, 2000 Office Action) - December 26, 2001]

41. (Twice Amended) A method of treating a human or animal so as to inhibit the function of a target RNA therein which method comprises administering a therapeutically effective amount of a modified nucleotide compound so as to inhibit the function of the target RNA, which modified RNase H resistant nucleotide compound includes at least one component selected from the group consisting of  $MN_3M$ ,  $B(N)_xM$  and  $M(N)_xB$  wherein:

N is a phosphodiester-linked modified or unmodified 2'-deoxynucleoside moiety; provided that at least one N is a phosphodiester-linked unmodified 2'-deoxynucleoside moiety;

M is a moiety that confers endonuclease resistance on said component and that contains at least one modified or unmodified nucleic acid base;

B is a moiety that confers exonuclease resistance to the terminus to which it is attached; and

x is an integer of at least 2.

51. (Twice Amended) A modified nucleotide compound which comprises at least one component selected from the group consisting of  $MN_3M$ ,  $B(N)_xM$  and  $M(N)_xB$  wherein:

N is a phosphodiester-linked modified or unmodified 2'-deoxynucleoside moiety; provided that at least one N is a phosphodiester-linked unmodified 2'-deoxynucleoside moiety;

M is a moiety that confers endonuclease resistance on said component and that contains at least one modified or unmodified nucleic acid base;

B is a moiety that confers exonuclease resistance to the terminus to which it is attached; and

x is an integer of at least 2.

Christine L. Brakel et al.

Serial No. 08/479,999

Filed: June 28, 1994

Page 6 [Amendment Under 37 C.F.R. §1.116 (In Response To The September 26, 2000 Office Action) - December 26, 2001]

Cancel claim 52.

\* \* \* \* \*

Christine L. Brakel et al.

Serial No. 08/479,999

Filed: June 28, 1994

Page 7 [Amendment Under 37 C.F.R. §1.116 (In Response To The September 26, 2000 Office Action) - December 26, 2001]

REMARKS

Reconsideration of this application is respectfully requested.

Claims 1-52 were previously pending. Replacement claims 1, 18, 19, 21, 37, 41 and 51 have been entered above. Claim 52 has been canceled. No claim has been added by this paper. Accordingly, claims 1-51 as amended hereinabove are presented for further examination on the merits.

Acknowledgement is made that the art unit designated for this application has been changed. Any and all future correspondence will henceforth be directed to Group Art Unit 1631.

In a sincere effort to define their invention more clearly and to narrow the issues on appeal or place claims in an allowable condition, Applicants have amended the claims above. The amendments have restored the originally claimed subject matter in the form of components selected from the group consisting of  $MN_3M$ ,  $B(N)_xM$  and  $M(N)_xB$ . Moreover, in amending the claims above, Applicants have also expunged the subject matter deemed new matter in the outstanding September 26, 2001 Office Action. The instantly recited components are supported variously in the specification, including the originally filed claims.

In addition, Applicants are also now covering those compositions as defined in the present claims which are modified RNase H resistant nucleotide compounds. The language "RNase H resistant" is also variously supported by Applicants' original disclosure.

Entry of the above amendments to the claims is believed to be appropriate and necessary. First, these amendments do not raise new issues that would require further consideration and/or search by the Examiner. In particular, the amendments to the independent claims (1, 21, 41 and 51) with respect to the

Christine L. Brakel et al.

Serial No. 08/479,999

Filed: June 28, 1994

Page 8 [Amendment Under 37 C.F.R. §1.116 (In Response To The September 26, 2000 Office Action) - December 26, 2001]

component(s) recited in Applicants' claimed modified RNase H resistant nucleotide compounds, serve to advance prosecution by addressing an issue or issues raised in the September 26, 2000 Office Action. Further, no issue of new matter is raised by the entry of these amendments, since the subject matter corresponds to the original disclosure, including the originally filed claims. Moreover, it is believed that the amendments will actually serve to place this application in better form for appeal by materially reducing or simplifying the issues for appeal. Finally, the amendments do not present additional claims; instead at least one claim (52) has been canceled in a sincere effort to advance prosecution. Entry of the above amendments to the claims is respectfully requested.

**The Rejection Under 35 U.S.C. §112, First Paragraph**

Claims 1-19, 21-39, 41, 51, and 52<sup>1</sup> stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the Office Action (pages 2-3), the Examiner stated:

The instant claims have been amended to now contain NEW MATTER. For example, claim 1 now recites several new components made up of various N, M, and B moieties. These arrangements of said components in line 3 of claim 1 have not been found as filed and thus are NEW MATTER. The closest component arrangements to these is present in claim 21 as filed but do not give written description of these arrangements. Claims 2-19, 21-39, 41, 51, and 52 also contain this NEW MATTER either directly or indirectly via dependence from a claim that explicitly contains it. This rejection is necessitated by amendment.

---

<sup>1</sup> Although they were uncertain as to the basis of the new matter rejection as it applied to claim 52, nevertheless Applicants have canceled claim 52 in a sincere effort to advance prosecution.

Christine L. Brakel et al.

Serial No. 08/479,999

Filed: June 28, 1994

Page 9 [Amendment Under 37 C.F.R. §1.116 (In Response To The September 26, 2000 Office Action) - December 26, 2001]

As indicated in their opening remarks above, Applicants have restored the originally disclosed and claimed components ( $MN_3M$ ,  $B(N)_xM$  and  $M(N)_xB$ ) into the claims at hand.

In view of the above claim language and foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection for new matter.

**The First Rejection Under 35 U.S.C. §102(b)**

Claims 1, 2, 4, 8, 12-14, 19, and 42-50 are rejected under 35 U.S.C. §102(b) as being anticipated by Miller et al.(1985). In the Office Action (page 3), the Examiner stated:

This rejection is reiterated and maintained from the previous office action, mailed 1/4/99. Applicants argue that Miller et al. neither discloses nor suggests not fully modifying all of the internal phosphodiester linkages and is silent on RNase H sensitivity. This RNase H resistance argument is confusing in that instant claim 1, for example, lacks any mention of RNase H resistance or not. Only claims 44 and 49 as rejected hereinunder cite any RNase H practice and these claims, such as specifically claim 44 directs RNase H resistance to what is complexed with the compound of claim 42 and not the compound itself. This argument is thus non-persuasive as being directed to a limitation that is not in the claims under rejection.

The anticipation rejection is respectfully traversed.

As indicated in the opening remarks above, the present claims are directed to modified *RNase H resistant* nucleotide compounds, which distinguishes from Miller et al.

Accordingly, in light of the above claim amendments, Applicants respectfully request reconsideration and withdrawal of the first anticipation rejection.

Christine L. Brakel et al.

Serial No. 08/479,999

Filed: June 28, 1994

Page 10 [Amendment Under 37 C.F.R. §1.116 (In Response To The September 26, 2000 Office Action) - December 26, 2001]

**The Second Rejection Under 35 U.S.C. §102(b)**

Claims 1-4, 12-14, and 42-50 stand rejected under 35 U.S.C. §102(b) as being anticipated by Stein et al.(1988). In the Office Action (page 4), the Examiner stated:

This rejection is reiterated and maintained from the previous office action, mailed 1/4/99. Applicants argue again as above regarding RNase H resistance. This argument has been responded to above and is equally applicable here and is reiterated here. Applicants then argue regarding partial internal modification that is not in Stein et al. This is non-persuasive as it is based on the NEW MATTER added to the instant claims. This rejection is reiterated in anticipation of removal of the NEW MATTER thus leaving the claims rejected as before.

The second anticipation rejection is respectfully traversed.

As indicated in the previous anticipation rejection, Applicants are now claiming modified RNase H resistant nucleotide compounds, which distinguishes their claimed invention from either of Miller et al. or the instant Stein et al.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the second anticipation rejection.

**The Rejection Under 35 U.S.C. §103(a)**

Claims 1-52 stand rejected under 35 U.S.C. §103 (a) as being unpatentable over Walder et al.(1988) in view of Miller et al. (4, 469, 863) and Inoue et al. (1988). In the Office Action (page 5), the Examiner stated:

This rejection is maintained and reiterated as given in the office action, mailed 1/4/99. Applicants argue based on the internal partial modification of the claimed compounds which has been noted above as being NEW MATTER. This rejection is reiterated in anticipation of removal of the NEW MATTER thus leaving the claims rejected as before.

Christine L. Brakel et al.

Serial No. 08/479,999

Filed: June 28, 1994

Page 11 [Amendment Under 37 C.F.R. §1.116 (In Response To The September 26, 2000 Office Action) - December 26, 2001]

The obviousness rejection is respectfully traversed.

Applicants respectfully submit that the combination of cited documents would not have rendered their now claimed invention obvious to a person of ordinary skill in the art at the time their invention was made.

Reconsideration and withdrawal of the obviousness rejection is respectfully requested.

**Submission of Art-Related Document**

Applicants' attorney and his assistant are searching for any additional art-related documents. Should any such document come to light, Applicants intend to submit them in a supplemental information disclosure statement as soon as an indication has been received that this application has been revived.

**Submission of Consolidation Amendment**

Applicants' attorney is consolidating all pending claims into a clean version. As soon as an indication has been received that the present application has been revived, the undersigned will submit a consolidation amendment including a clean version of the pending claims.

\* \* \* \* \*

Christine L. Brakel et al.

Serial No. 08/479,999

Filed: June 28, 1994

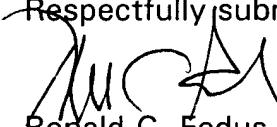
Page 12 [Amendment Under 37 C.F.R. §1.116 (In Response To The September 26, 2000 Office Action) - December 26, 2001]

**SUMMARY AND CONCLUSIONS**

Claims 1-51 as amended hereinabove are presented for further examination on the merits. Replacement claims 1, 18, 19, 21, 37, 41 and 51 have been entered above. Claim 52 has been canceled. No claim has been added by this paper.

This Amendment is accompanied by a Petition Under 37 C.F.R. §1.137(b) and authorization for the fee therefor. No other fee is believed due in connection with this Amendment, including any claim fee since one claim has been canceled and no claims have been added. If any other fee or fees are due, however, the Patent and Trademark Office is authorized to charge the amount of any such fee(s) to Deposit Account No. 05-1135, and to credit any overpayment thereto.

In view of the above discussion of the issues and amendments to the claims, Applicant respectfully submits that all of the instant claims are in allowable condition. Should it be deemed helpful or necessary, the Examiner is respectfully invited to telephone the undersigned at (212) 583-0100 to discuss the subject application.

Respectfully submitted,  
  
Ronald C. Fedus  
Registration No. 32,567  
Attorney for Applicant

ENZO THERAPEUTICS, INC.  
c/o Enzo Biochem, Inc.  
527 Madison Avenue, 9<sup>th</sup> Floor  
New York, New York 10017  
Tel.: (212) 583-0100  
Fax.: (212) 583-0150

**RECEIVED**  
JAN 08 2002  
**OFFICE OF PETITIONS**



CHRISTINE L. BRAKE ET AL., U.S. PAT. APPL. SER. NO. 08/479,999  
MARKED-UP VERSION OF THE AMENDED CLAIMS  
Exhibit A [Amendment Under 37 C.F.R. §1.116 -- December 26, 2001]

1. (Four Times Amended) A modified RNase H resistant nucleotide compound which includes at least one component selected from the group consisting of  $MN_3M$ ,  $\{N\}_xM(N)_y$ ,  $\{N\}_xM(N)_yM$ ,  $B\{N\}_xM(N)_y$ , and  $\{N\}_xM(N)_yB$   $B(N)_xM$  and  $M(N)_xB$  wherein

N is a phosphodiester-linked modified or unmodified 2'-deoxynucleoside moiety; provided that at least one N is a phosphodiester-linked unmodified 2'-deoxynucleoside moiety;

M is a moiety that confers endonuclease resistance on said component and that contains at least one modified or unmodified nucleic acid base;

B is a moiety that confers exonuclease resistance to the terminus to which it is attached; and

x is an integer of at least 2[; and

~~y is an integer].~~

18. (Twice Amended) The modified nucleotide compound of claim 1 which includes at least one sequence of the formula  $\{N\}_yM(N)_xB$   $M(N)_xB$  wherein B is modified or unmodified 2',3'-dideoxyribose nucleotide.

19. (Twice Amended) The modified nucleotide compound of claim 1 wherein  $[y] x$  is an integer selected from the group consisting of 2 or 2.

RECEIVED  
JAN 08 2002  
OFFICE OF PETITIONS

21. (Four Times Amended) A method of inhibiting the function of an RNA, which comprises:

contacting said RNA, under conditions permissive of hybridization, with a modified RNase H resistant nucleotide compound which includes at least one complementary component selected from the group consisting of  $MN_3M$ ,  $[(N)_xM(N)_y, (N)_xM(N)_yM, B(N)_xM(N)_y, \text{ and } (N)_xM(N)_yB]$  B(N)<sub>x</sub>M and M(N)<sub>x</sub>B wherein:

$N$  is a phosphodiester-linked modified or unmodified 2'-deoxynucleoside moiety; provided that at least one  $N$  is a phosphodiester-linked unmodified 2'-deoxynucleoside moiety;

$M$  is a moiety that confers endonuclease resistance on said component and that contains at least one modified or unmodified nucleic acid base;

$B$  is a moiety that confers exonuclease resistance to the terminus to which it is attached; and

$x$  is an integer of at least 2[; and

~~y is an integer~~].

37. (Twice Amended) The method of claim 21 wherein the RNA is contacted with a compound which includes at least one sequence of the formula  $[(N)_xM(N)_yB]$  M(N)<sub>x</sub>B wherein  $B$  is modified or unmodified 2',3'-dideoxyribose nucleotide.

41. (Twice Amended) A method of treating a human or animal so as to inhibit the function of a target RNA therein which method comprises administering a therapeutically effective amount of a modified nucleotide compound so as to inhibit the function of the target RNA, which modified RNase H resistant nucleotide compound includes at least one component selected from the group consisting of

Christine L. Brakel et al.

Serial No.: 08/479,999

Filed: June 28, 1994

Page 3 [(Exhibit A to Amendment Under 37 C.F.R. §1.116 --

Marked-Up Version of Claims) - December 26, 2001]

$MN_3M$ ,  $\{N\}_xM\{N\}_y$ ,  $\{N\}_xM\{N\}_yM$ ,  $B(N)_xM\{N\}_y$ , and  $\{N\}_xM\{N\}_yB$ ] B(N)<sub>x</sub>M and M(N)<sub>x</sub>B

wherein:

N is a phosphodiester-linked modified or unmodified 2'-deoxynucleoside moiety; provided that at least one N is a phosphodiester-linked unmodified 2'-deoxynucleoside moiety;

M is a moiety that confers endonuclease resistance on said component and that contains at least one modified or unmodified nucleic acid base;

B is a moiety that confers exonuclease resistance to the terminus to which it is attached; and

x is an integer of at least 2[; and

y is an integer].

51. (Twice Amended) A modified nucleotide compound which comprises at least one component selected from the group consisting of  $MN_3M$ ,  $\{N\}_xM\{N\}_y$ ,  $\{N\}_xM\{N\}_yM$ ,  $B(N)_xM\{N\}_y$ , and  $\{N\}_xM\{N\}_yB$ ] B(N)<sub>x</sub>M and M(N)<sub>x</sub>B wherein:

N is a phosphodiester-linked modified or unmodified 2'-deoxynucleoside moiety; provided that at least one N is a phosphodiester-linked unmodified 2'-deoxynucleoside moiety;

M is a moiety that confers endonuclease resistance on said component and that contains at least one modified or unmodified nucleic acid base;

B is a moiety that confers exonuclease resistance to the terminus to which it is attached; and

x is an integer of at least 2[; and

y is an integer].

\* \* \* \* \*

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant(s): Christine L. Brakel et al.

Serial No. 08/479,999

Group Art Unit: 1631

Filed: June 28, 1994

Ex'r: Ardin H. Marschel, Ph.D.

Title: MODIFIED NUCLEOTIDE COMPOUNDS (As Previously Presented)

**FILED VIA EXPRESS MAIL**

Honorable Commissioner of  
Patents and Trademarks  
Washington, D. C. 20231

Sir:

Transmitted herewith is an Amendment Under 37 C.F.R. §1.116 (In Response To The September 26, 2000 Office Action) in the above-identified patent application.

The fee\* has been calculated as shown below:

	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	ADDITIONAL FEE
Total	51	Minus	52	=0	X \$9	\$ 0.00
Indep	5	Minus	6	=0	X \$42	\$ 0.00
( )	First Presentation of Multiple Dependent Claims				\$ 140	\$ 0.00
	TOTAL ADDITIONAL FEE					\$ 0.00

\*Small entity status was previously established in this application and is still applicable.

Charge Deposit Account No. 05-1135 in the amount of \$ \_\_\_\_\_

A check in the amount of \$ \_\_\_\_\_ is attached.

The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 05-1135 any filing fees under 37 C.F.R. §1.16 for the presentation of extra claims and any patent application processing fees under 37 C.F.R. §1.17.

Copies are being provided in triplicate.

**RECEIVED**

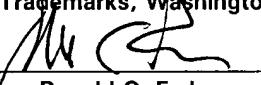
JAN 08 2002

Enz-47(C2)

OFFICE OF PETITIONS

Christine L. Brakel et al.  
Serial No.: 08/479,999  
Filed: June 28, 1994  
Page 2 (Transmittal -- December 26, 2001)

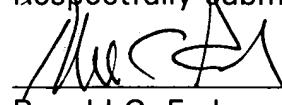
---

EXPRESS MAIL CERTIFICATE	
"Express Mail" Label No. <u>EL491424303US</u>	
Deposit Date	<u>December 26, 2001</u>
I hereby certify that this paper and the attachments herein are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington DC 20231.	
	<u>DCC 26 2001</u>
Ronald C. Fedus	Date
Reg. No. 32,567	

Christine L. Brakel et al.  
Serial No.: 08/479,999  
Filed: June 28, 1994  
Page 3 (Transmittal -- December 26, 2001)

Also enclosed: Petition Under 37 C.F.R. § 1.137(b) & Notice of Appeal.

Respectfully submitted,

  
Ronald C. Fedus  
Registration No. 32,567  
Attorney for Applicant(s)

December 26, 2001  
Date  
  
ENZO THERAPEUTICS, INC.  
c/o Enzo Biochem, Inc.  
527 Madison Avenue (9<sup>th</sup> Fl.)  
New York, New York 10022  
Tel. (212) 583-0100

Attorney's Docket No.: Enz-47(C2)

Enz-47(C2)